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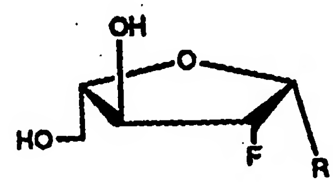
(54) Title: L-NUCLEOSIDES FOR THE TREATMENT OF HEPATITIS B-VIRUS AND EPSTEIN-BAR VIRUS

(57) Abstract



(I)

A method for the treatment of a host, and in particular, a human, infected with HBV or EBV is provided that includes administering an HBV- or EBV- treatment amount of an L-nucleoside of formula(I) wherein R is a purine or pyrimidine base. In one preferred embodiment, the active compound is 2'-fluoro-5-methyl-β-L-arabinofuranosyluridine (also referred to as L-FMAU). This compound is a potent antiviral agent against HBV and EBV and exhibits low cytotoxicity. Other specific examples of active compounds include N_1-(2'-deoxy-2'-fluoro-β-L-arabinofuranosyl)-5-ethyluracil, N_1-(2'-deoxy-2'-fluoro-β-L-arabinofuranosyl)-5-iodocytosine), and N_1-(2'-deoxy-2'-fluoro-β-L-arabinofuranosyl)-5-iodouracil.

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L-NUCLEOSIDES FOR THE TREATMENT OF HEPATITIS B-VIRUS AND EPSTEIN-BAR VIRUS

This invention is in the area of methods for the treatment of hepatitis B virus (also referred to as "HBV") and Epstein-Bar Virus (referred to as "EBV") that includes administering an effective amount of one or more of the active compounds disclosed herein, or a pharmaceutically acceptable derivative or prodrug of one of these compounds.

Background of the Invention

Hepatitis B virus has reached epidemic levels worldwide. After a two to six month incubation period in which the host is unaware of the infection, HBV infection can lead to acute hepatitis and liver damage, that causes abdominal pain, jaundice, and elevated blood levels of certain enzymes. HBV can cause fulminant hepatitis, a rapidly progressive, often fatal form of the disease in which massive sections of the liver are destroyed. Patients typically recover from acute viral hepatitis. In some patients, however, high levels of viral antigen persist in the blood for an extended, or indefinite, period, causing a chronic infection. Chronic infections can lead to chronic persistent hepatitis. Patients infected with chronic persistent HBV are most common in developing countries. By mid-1991, there were approximately 225 million chronic carriers of HBV in Asia alone, and worldwide, almost 300 million carriers. Chronic persistent hepatitis can cause fatigue, cirrhosis of the liver, and hepatocellular carcinoma, a primary liver cancer.

In western industrialized countries, high risk

groups for HBV infection include those in contact with HBV carriers or their blood samples. The epidemiology of HBV is in fact very similar to that of acquired immunodeficiency syndrome, which accounts for why HBV infection is common among patients with AIDS or HIV-associated infections. However, HBV is more contagious than HIV.

HBV is second only to tobacco as a cause of human cancer. The mechanism by which HBV induces cancer is unknown, although it is postulated that it may directly trigger tumor development, or indirectly trigger tumor development through chronic inflammation, cirrhosis, and cell regeneration associated with the infection.

The Epstein-Barr virus (EBV) is a member of the genus *Lymphocryptovirus*, which belongs to the subfamily gammaherpesvirinae. It is notably lymphotropic. EBV has the classic structure of herpesviruses, viz., its double-stranded DNA genome is contained within an icosapentahedral nucleocapsid, which, in turn, is surrounded by a lipid envelope studded with viral glycoproteins. An amorphous tegument protein occupies the space between the envelope and the nucleocapsid.

All human herpesviruses infect and replicate within lymphocytes to some extent, but EBV does so efficiently. Most importantly, the pathogenesis and host responses to infection with EBV are more dependent upon lymphocytic infection than is evident with the other human herpesviruses.

EBV is now recognized as a cause of B-cell lymphoproliferative diseases, and has been linked to a variety of other severe and chronic illnesses, including a rare progressive mononucleosis-like syndrome and oral hairy leukoplakia in AIDS patients. The suggestion that EBV is a major cause of chronic fatigue has not withstood scrutiny.

EBV is primarily transmitted through the saliva, although some infections are transmitted by blood transfusion. More than 85% of patients in the acute phases of infectious mononucleosis secrete EBV.

EBV has been associated with cancer. At least two groups of patients are at risk for development of EBV-associated lymphomas: those who have received transplants of kidney, heart, bone marrow, liver, or thymus under the cover of immunosuppressive therapy, and patients with AIDS. EBV-associated cancers include Burkitt's Lymphoma and Nasopharyngeal Carcinoma.

In light of the fact that hepatitis B virus and Epstein-Barr virus have severe and often tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat humans infected with the viruses that have low toxicity to the host.

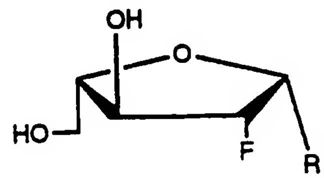
Therefore, it is an object of the present invention to provide a compound, composition, and method for the treatment of hepatitis B virus.

It is another object of the present invention to provide a compound, composition, and method for the treatment of Epstein Barr virus.

SUMMARY OF THE INVENTION

A method for the treatment of a host, and in particular, a human, infected with HBV or EBV is provided that includes administering an HBV- or

EBV-treatment amount of an L-nucleoside of the formula:



wherein R is a purine or pyrimidine base. In a preferred embodiment, the nucleoside is provided as the indicated enantiomer and substantially in the absence of its corresponding enantiomer (i.e., in enantiomerically enriched, including enantiomerically pure form).

In one preferred embodiment, the active compound is 2'-fluoro-5-methyl-ß-L-arabinofuranosyluridine (also referred to as L-FMAU). This compound is a potent antiviral agent against HBV and EBV and exhibits low cytotoxicity. Other specific examples of active compounds include N_1-(2'-deoxy-2'-fluoro-ß-L-arabinofuranosyl)-5-ethyluracil, N_1-(2'-deoxy-2'-fluoro-ß-L-arabinofuranosyl)-5-iodocytosine), and N_1-(2'-deoxy-2'-fluoro-ß-L-arabinofuranosyl)-5-iodouracil.

In an alternative embodiment, an L-nucleoside is provided for use in the treatment of HBV or EBV that contains a 2'-arabino-hydroxyl group, for example, L-arathymidine, L-fludarabine, L-ara-guanosine, and L-ara-inosine, as illustrated in Figure 1.

The L-nucleosides disclosed herein and their pharmaceutically acceptable derivatives or pharmaceutically acceptable formulations containing these compounds are useful in the prevention and treatment of HBV infections and other related conditions such as anti-HBV antibody positive and

HBV-positive conditions, chronic liver inflammation caused by HBV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. The compounds can likewise be used in the treatment of EBV-associated disorders. These compounds or formulations can also be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HBV or anti-EBV antibody or HBV- or EBV-antigen positive or who have been exposed to HBV or EBV.

In another embodiment, the active compound or its derivative or salt can be administered in combination or alternation with another anti-HBV agent or anti-EBV agent, including those listed above, or an anti-HIV agent. In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include the (-)-enantiomer of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane

(3TC); carbovir, acyclovir, interferon, AZT, DDI (2',3'-dideoxyinosine), DDC (2',3'-dideoxycytidine), L-DDC, L-5-F-DDC and D4T.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is an illustration of selected L-nucleosides that fall within the present invention: L-FMAU (2'-fluoro-5-methyl-ß-L-arabinofuranosyluridine), L-FIAU (2'-fluoro-5-iodo-ß-L-arabinofuranosyluridine), L-FC (2'-fluoro-ß-L-arabinofuranosylcytosine), L-FIAC (2'-fluoro-5-iodo-ß-L-arabinofuranosylcytosine), L-2-Cl-2'-F-2'-deoxyadenine, L-FEAU (2'-fluoro-5-ethyl-ß-L-arabinofuranosyluridine), L-arathymidine, L-fludarabine, L-araguanosine, and L-ara-inosine.

Figure 2 is a graph of the percentage of viable cells versus drug concentration of L-FMAU in H1 cells.

Figure 3 is a schematic illustration of the preparation of 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-L-ribofuranose (compound 10).

Figure 4 is a schematic illustration of an alternative preparation of 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-L-ribofuranose (compound 10).

Figure 5 is a schematic illustration of a method for the preparation of 1,3,5-tri-O-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranose (compound 13).

Figure 6 is schematic illustration of a method for the preparation of N_9-[3',5'-di-O-benzoyl-2'-deoxy-2'-fluoro-ß-L-arabinofuranosyl]-2,6-di-chloropurine (compound 15) and N_9-[2'-deoxy-2'-fluoro-ß-L-arabinofuranosyl]-2,6-di-chloropurine (compound 16).

Figure 7 is an illustration of a method for the preparation of a number of 2'-deoxy-2'-fluoro-ß-L-arabinofuranosyl]-pyrimidines (compounds 17-24).

Figure 8 is an illustration of a method for the preparation of N_1-(2'-deoxy-2'-fluoro-ß-L-arabinofuranosyl)-5-iodocytosine) (compound 22).

Figure 9 is an illustration of a method for the preparation of 9-ß-L-arabinofuranosyladenine.

Figure 10 is an illustration of an alternative route for the preparation of 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-L-ribofuranose (compound 10) from 1,2-di-O-isopropylidene-α-L-xylofuranose (compound 3).

Figure 11 is a graph of the plasma concentration of L-(-)-FMAU in mice after oral administration over time (cross, 10 mg/kg administered bid (bi-daily) for 29 days prior to pharmacokinetic study and then study carried out on day thirty on administration of same concentration; dark circle, 50 mg/kg administered bid for 29 days prior to study and then study carried out on day thirty on administration of same concentration; open circle, 50 mg/kg administered for the first time on the first day of the study).

Figure 12 is a graph of the concentration of L-(-)-FMAU in mouse liver after oral administration over time (cross, 10 mg/kg administered bid (bi-daily) for 30 days prior to pharmacokinetic study and then study carried out on day thirty one on administration of same concentration; dark circle, 50 mg/kg administered bid for 30 days prior to study and then study carried out on day thirty one on administration of same concentration; open circle, 50 mg/kg administered for the first time on the first day of the study).

Figure 13a illustrates the change in body weight over thirty days of control BDF1 female mice. Figures 13b and 13c illustrate the change in body weight over thirty days of BDF1 female mice dosed with 10 mg/kg bid (13b) and 50 mg/kg (13c)

L-(-)-FMAU. The body weight presented represents the mean and standard deviation of that of five to seven mice.

Figures 14-20 provide the clinical chemistry of mouse plasma after administration of L-(-)-FMAU at 10 mg/kg (three mice) or 50 mg/kg (three mice) bid for thirty days. Figure 14 is a bar chart graph of the concentration of total bilirubin in the mouse plasma in mg/dL. Figure 15 is a bar chart graph of the concentration of alkaline phosphatase in the mouse plasma in U/L. Figure 16 is a bar chart graph of the concentration of creatinine in the mouse plasma in mg/dL. Figure 17 is a bar chart graph of the concentration of AST (SGOT, serum glutamic oxalic transaminase) in the mouse plasma in U/L. Figure 18 is a bar chart graph of the concentration of ALT (SGPT, serum glutamic pyruvic transaminase) in the mouse plasma in U/L. Figure 19 is a bar chart graph of the concentration of lactic acid in the mouse plasma in mmol/L. Figure 20 is a bar chart graph of the concentration of lactic dehydrogenase in the mouse plasma in U/L.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "enantiomerically enriched" refers to a nucleoside composition that includes at least approximately 95%, and preferably approximately 97%, 98%, 99%, or 100% of a single enantiomer of that nucleoside.

As used herein, the term alkyl specifically includes but is not limited to C_1 to C_{10} alkyl groups, including methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, t-butyl, isopentyl, amyl, t-pentyl, cyclopentyl, and cyclohexyl.

As used herein, the term acyl specifically includes but is not limited to acetyl, propionyl, butyryl, pentanoyl, 3-methylbutyryl, hydrogen succinate, 3-chlorobenzoate, benzoyl, acetyl, pivaloyl, mesylate, propionyl, valeryl, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, and oleic.

As used herein, and unless otherwise defined, the term aryl refers to phenyl.

The term "protected" as used herein and unless otherwise defined refers to a group that is added to an oxygen or nitrogen atom to prevent its further reaction during the course of derivatization of other moieties in the molecule in which the oxygen or nitrogen is located. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis.

The term purine or pyrimidine base includes, but is not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkaryl, or aralkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-thioalkyl purine, thymine, cytosine, 6-azapyrimidine, 2-mercaptopyrmidine, uracil, N^5-alkylpyrimidines, N^5-benzylpyrimidines, N^5-halopyrimidines, N^5-vinylpyrimidine, N^5-acetylenic pyrimidine, N^5-acyl pyrimidine, N^5-hydroxyalkyl purine, N^6-thioalkyl purine, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-

butyldiphenylsilyl, tritylmethyl, alkyl groups, acyl groups such as acetyl, propionyl, butyl, methylsulfonyl, and p-toluylsulfonyl. It specifically includes 5-methyl uracil (thymine), 5-iodouracil, cytosine, and 5-ethyluracil.

The invention as disclosed herein is a method and composition for the treatment of HBV infection, EBV infection, and other viruses replicating in a like manner, in humans or other host animals such as HIV, that includes administering an effective amount of one or more of the above-identified L-nucleosides, or a physiologically acceptable derivative, or a physiologically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. The compounds of this invention either possess anti-HBV activity, anti-EBV-activity, or are metabolized to a compound or compounds that exhibit anti-HBV or anti-EBV activity. The compounds disclosed herein can also be used to treat HBV and EBV associated disorders.

The active compound can be administered as any derivative that upon administration to the recipient, is capable of providing directly or indirectly, the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and the 5' and purine or pyrimidine acylated or alkylated derivatives of the active compound (alternatively referred to as "physiologically active derivatives"). In one embodiment, the acyl group is a carboxylic acid ester (i.e., -C(O)R') in which the non-carbonyl moiety (R') of the ester group is selected from straight, branched, or cyclic C_1 to C_{10} alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including

phenyl optionally substituted with halogen, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl or benzyl group. The alkyl group can be straight, branched, or cyclic, and is optimally a C_1 to C_{10} group.

I. Synthesis of L-Nucleosides

The L-nucleosides disclosed herein can be prepared as described in detail below, or by other assays known to those skilled in the art.

In the synthetic schemes described below, other standard reagents, including equivalent acids, bases, and solvents can be used in place of those named, as known to those of ordinary skill in the art. A wide range of protecting groups for oxygen or nitrogen can be used, and are disclosed, for example, in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991. Suitable oxygen and nitrogen protecting groups, include, for example, a trisubstituted silyl group such as trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, trityl, alkyl group, acyl groups such as acetyl, propionyl, benzoyl, p-NO_2 benzoyl, benzyl, or toluyl, methylsulfonyl, or p-toluylsulfonyl. Functional oxygen and nitrogen groups on the heterocyclic base should be protected before condensation with the sugar.

Suitable reducing agents include $NaBH_4$, diisobutylaluminum hydride (DIBAL-H), lithium borohydride ($LiBH_4$), and sodium bis(2-

methoxyethoxy)-aluminum hydride (Red-Al). Suitable oxidizing agents include aqueous acidic chromic acid (CrO_3), sodium dichromate (Na_2CrO_7), pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), potassium permanganate ($KMnO_4$), lead tetraacetate/ pyridine, oxygen over a platinum/carbon catalyst, RuO_4, $RuO_4/NaIO_4$, dimethylsulfoxide/dicyclohexyl-carbodiimide (DMSO/DCC) and a proton donor, silver carbonate, triphenylbismuth carbonate, Oppenauer oxidation (aluminum alkoxides in acetone) and manganese dioxide (for selective oxidation of allylic or benzylic alcohols in the presence of other alcohols).

Friedel-Crafts catalysts (Lewis acids) that can be used in the condensation reaction include $SnCl_4$, $ZnCl_4$, $TiCl_4$, $AlCl_3$, $FeCl_3$, BF_3-diethylether, and BCl_3. These catalysts require anhydrous conditions because the presence of water reduces their activity. The catalysts are also inactivated in the presence of organic solvents with active hydrogens, such as alcohols and organic acids. The catalysts are typically used in solvents such as carbon disulfide, methylene chloride, nitromethane, 1,2-dichloroethane, nitrobenzene, tetrachloroethane, chlorobenzene, benzene, toluene, dimethylformamide, tetrahydrofuran, dioxane, or acetonitrile. Anhydrous aluminum chloride is not soluble in carbon disulfide. Niedballa, et al., J. Org. Chem. 39, 25 (1974). The preferred catalyst is $SnCl_4$. The preferred solvent is 1,2-dichloroethane. Trimethylsilyl triflate can be used under the same conditions described above for the Friedel-Crafts catalysts. The reaction proceeds at a temperature range of from -10°C to 200°C. Desilylation can be carried out with a variety of reagents, including acetic acid, trifluoroacetic acid, hydrogen fluoride, n-

tetrabutylammonium fluoride, potassium fluoride and pyridinium HCl.

Referring to Figure 3, starting from L-xylose (1a), the key intermediate 1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose (10) was synthesized in a total yield of 20% (L. Vargha, *Chem. Ber.*, 1954, 87, 1351; Holy, A., et al., *Synthetic Procedures in Nucleic Acid Chemistry*, V1, 163-67). As shown in Figure 4, compound 10 can also be synthesized from the more expensive starting material L-ribose (Holy, A., et al., *Synthetic Procedures in Nucleic Acid Chemistry*, V1, 163-67). Figure 3 illustrates an alternative synthesis of compound 10 (yield of 53%), which was subsequently fluorinated at C_2 (*J. Org. Chem.*. 1985, 50, 3644-47) to obtain 1,3,5-tri-O-benzoyl-2-deoxy-2-fluoro-L-arabinofuranose (13), which was condensed with different bases through the bromosugar to provide the 2'-deoxy-2'-fluoro-arabinofuranosyl nucleosides in various yields.

1,2-Di-O-isopropylidene-α-L-xylofuranose (3)

To 650 ml of anhydrous acetone was added 4 ml of conc. sulfuric acid, 5 g of molecular sieve (4A), 80 g of anhydrous cupric sulfate and 50 g of L-xylose and the mixture was stirred at room temperature for 36 hours. The reaction mixture was filtered and washed thoroughly with acetone, the combined filtrate was neutralized with ammonium hydroxide then evaporated to dryness. Ethyl acetate (200 ml) was added, then filtered and evaporated, yielded an oil which was dissolved in 250 ml of 0.2% HCl solution and stirred at room temperature for 2.5 hours. The pH was adjusted to 8 with sat. $NaHCO_3$, then evaporated to dryness, the residue was extracted with ethyl acetate. Removal of the solvent provided a yellow oil of compound 3 (41.7g, 82.3%).

^{1}H-NMR($CDCl_3$): δ 5.979 (d, J=3.78Hz,1H, H-1); 4.519(d, J=3.6Hz, 1H, H-2);4.308(bd, 1H, H-3); 4.080(m, 3H, H-4 and H-5); 1.321(s, 3H, CH_3); 1.253 (s, 3H, CH_3).

1,2-Di-O-isopropylidene-3,5-di-O-o-tolylsulfonyl-α-L-xylofuranose (4)

Compound 3 (40 g, 210 mmol) was stirred in 500 ml of anhydrous pyridine at 0°C, while TsCl (75 g, 393 mmol) was dissolved in 100 ml of $CHCl_3$ was added dropwise. After 3 hours, another portion of TsCl (50 g, 262 mmol) in 50 ml of $CHCl_3$ was added the same as above. The mixture was stirred at r.t. for 24 hrs, then chilled at 0°C, water (10 ml) was added, then stirred at r.t. for 30 minutes. The reaction mixture was poured into 500 ml of ice-water, extracted with $CHCl_3$ (150 ml x 4), washed with 1.5M H_2SO_4 (150 ml x 4), sat.$NaHCO_3$ (200 ml x 2), dried ($MgSO_4$). Removing solvent gave a brown syrup, which upon crystallization from EtOH, gave 4 as a white solid (103.8g, 99%).

^{1}H-NMR($CDCl_3$): δ 7.282, 7.836 (m, 8H, OTs); 5.849 (d, J=3.51Hz, 1H, H-1); 4.661, 4.779 (m, 2H, H-3 and H-4); 4.193(dd, 1H, H-2); 4.011 (d, 2H, H-5); 2.448, 2.478 (2s, 6H, -OTs); 1.261, 1.320 (2s, 6H, CH_3).

1,2-Di-O-acetyl-3,5-di-O-p-tolylsulfonyl-α,β-xylofuranose (5)

Compound 4(70 g, 140.5 mmol) was dissolved in 700 ml of glacial AcOH and 100 ml of Ac_2O while 50 ml of conc. sulfuric acid was added dropwise at 0°C. The resulting solution was stirred at r.t overnight and then poured into 1L of ice-water, extracted with $CHCl_3$ (200 ml x 4), washed with sat. $NaHCO_3$, dried ($MgSO_4$). After removing solvent in

vacuo, gave 5 as a syrup (84.2 g, crude yield 110%).

Methyl-3,5-di-O-p-tolylsulfonyl-α,β-xylofuranose (6)

The crude 5 (80 g) was stirred in 500 ml of 1% HCl/CH_3OH at r.t. for 30 hrs. The solvent was removed under reduced pressure, the residue dissolved in 300 ml of $CHCl_3$, washed with sat. $NaHCO_3$, dried ($MgSO_4$). Removal of solvent gave 6 as a syrup (60 g, 90% from 4).

Methyl-2-O-benzoyl-3,5-di-O-p-tolylsulfonyl-α,β-xylofuranoside (7)

The syrup 6 (60 g, 127 mmol) was dissolved in 200 ml of pyridine and stirred at 0°C, while benzoyl chloride (40 ml, 345 mmol) was added dropwise, the resulting solution was stirred at r.t. for 17 hrs. It was concentrated to about 50 ml, then poured into 300 ml of ice-water, extracted with $CHCl_3$, washed with 3N H_2SO_4 and sat. $NaHCO_3$, dried ($MgSO_4$). After evaporation of the solvent, gave 7 as a syrup (71 g, 97%).

Methyl-2,3,5-tri-O-benzoyl-α-β-L-ribofuranoside (9)

The syrup 7 (70 g) and sodium benzoate (100 g, 694 mmol) were suspended in 1200 ml of DMF and mechanically stirred under reflux for 16 hrs. It was cooled to r.t. and then poured into 1L of ice-water, extracted with ether, dried ($MgSO_4$). Evaporation of solvent gave a syrup (50 g, 8a and 8b), which was dissolved in 180 ml of pyridine and benzoylated (BzCl, 20 ml, 172 mmol) for 17 hrs at r.t. After work up, gave 9 as a brown syrup (48 g, 83% from 7).

1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose (10)

Compound 9 (26 g, 54.6 mmol) was treated with 275 ml of glacial acetic acid, 55 ml of acetic anhydride and 16 ml of conc. sulfuric acid at 0°C to r.t. for 17 hrs. Then poured into 1L of ice-water, extracted with chloroform (200 ml x 4). The combined extract was washed with sat. $NaHCO_3$ and dried ($MgSO_4$). Removing solvent gave a brown syrup which was treated with ethanol to give 10 as a white solid. (8.8 g, 32%). m.p. 124.7°C, lit. 129-130°C; D from: 130-131°C $[\alpha]_D$=-45.613 (c 1.0, $CHCl_3$), D form: $[\alpha]_D$=+44.2.

^{1}H-NMR($CDCl_3$): δ 7.317, 8.134 (m, 15H, OBz); 6.437 (s, 1H, H-1); 5.835 (m, 2H, H-2 and H-3); 4,649 (m, 3H, H-4 and H-5); 2.003(s, 3H, $\underline{CH_3}$COO-).

1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose (from L-ribose)

L-Ribose (5 g, 33.3 mmol) was suspended in 120 ml of 1% HCl/MeOH and stirred at r.t. for 3 hrs, when a clear solution was obtained. The reaction was quenched by adding 30 ml of anhydrous pyridine, then evaporated under reduced pressure. The resulting syrup was coevaporated with pyridine (30 ml x 2), then dissolved in 80 ml of anhydrous pyridine, and stirred at 0°C while benzoyl chloride (20 ml, 172 mmol) was added dropwise. After stirring at r.t. for 17 hrs, the reaction was complete. Water (10 ml) was added and the mixture was stirred at r.t. for 0.5 hr, then concentrated to about 50 ml, poured into 150 ml of ice-water, extracted with chloroform (50 ml x 4), washed successively with 3N H_2SO_4 (30 ml x 2), sat. $NaHCO_3$ (30 ml x 3), and dried ($MgSO_4$). Removal of the solvent gave 9 as a syrup of 13 g.

The crude 9 was dissolved in 80 ml of HBr/AcOH (45%, w/v) and stirred at r.t. for 1.5 hrs. To this mixture was added glacial acetic acid (50 ml) and the resulting solution stirred at 0°C, while 34 ml of water was added slowly to keep the temperature below 7°C. It was then stirred at r.t. for 1 hr, poured into 200 ml of ice-water, extracted with chloroform (50 ml x 5). The combined extracts were washed with sat. $NaHCO_3$, dried ($MgSO_4$). Removal of solvent gave a syrup (13g), which was dissolved in 40 ml of anhydrous pyridine, stirred at 0°C. Acetic anhydride (14 ml, 148.4 mmol) was then added dropwise. After the reaction was completed, it was poured into 150 ml of ice-water, extracted with chloroform (50 ml x 4), washed successively with 3N H_2SO_4 (30 ml x 2), sat. $NaHCO_3$ (50 ml x 2), and dried ($MgSO_4$). Removal of solvent and treatment with methanol gave 10 as a white solid (9.2 g, 53.7% from L-ribose).

1,3,5-Tri-O-benzoyl-α-L-ribofuranose (11)

Compound 10 (9 g, 17.84 mmol) was stirred in 100 ml of CH_2Cl_2 at 0°C while 70 ml of CH_2Cl_2 containing HBr (3.2 g, 30.5 mmol) was added in one portion. The mixture was stirred at 0°C for 3.5 hrs, water (55 ml) was added and the mixture stirred at r.t. for 18 hrs. The organic layer was separated, washed with sat. $NaHCO_3$, and dried ($MgSO_4$). After evaporation of the solvent, a foam was obtained, which upon recrystallization from CH_2Cl_2 and n-hexane, gave 11 as a white solid. (6.2 g, 75.5%). m.p. 137-138°C, lit. 140-141°C, $[\alpha]_D$=-81.960 (c 0.55, $CHCl_3$; D form: $[\alpha]_D$=+83.71.

^{1}H-NMR($CDCl_3$): δ 7.312, 8.187 (m, 15H, OBz); 6.691 (d, J=4.59Hz, H-1); 5.593 (dd, $J_{4\text{-}3}$=6.66Hz; $J_{2\text{-}3}$=1.8Hz, 1H, H-30; 4.637, 4.796 (m, 4H, H-2, H-4 and H-5); 2.3 (b, OH).

1,3,5-Tri-O-benzoyl-2-O-imidazosulfuryl-α-L-ribofuranose (12)

Compound 11 (5.94 g, 12.84 mmol) was stirred in 50 ml of anhydrous CH_2Cl_2 at -15°C (dry ice-CCl_4). Anhydrous DMF (15 ml) and sulfuryl chloride (3.2 ml, 3.98 mmol) was added sequentially. The solution was stirred at -15°C for 30 minutes and then left at r.t. for 4 hrs. Imidazole (8.7 g, 12.78 mmol) was added in three portions while the reaction mixture was cooled in an ice bath. It was then stirred at r.t. for 17 hrs. The mixture was poured into 150 ml of ice-water and the water phase extracted with CH_2Cl_2 (50 ml x 3). The combined organic layer was washed with water and dried ($MgSO_4$). Purification by column (hexane:EtOAc/5:1-1:1) gave 12 as a white solid (3.7g, 49%). m.p. 124.5-125.5°C, lit: 129°C; $[\alpha]_D$=-68.976; D form: +66.154.

^{1}H-NMR($CDCl_3$): δ 6.9, 8.2 (m, 18H, Ar-H); 6.67 (d, J=4.4Hz, 1H, H-1); 5.59 (dd, 1H, H-3), 5.21 (dd, 1H, H-2); 4.5, 4.8 (m, 3H, H-4 and H-5).

1,3,5-Tri-O-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranose (13).

A suspension of 12 (3.33 g, 5.62 mmol), KHF_2 (1.76 g, 22.56 mmol) in 30 ml of 2,3-butanediol was stirred under argon. It was heated to 150°C while 1 ml of HF/H_2O (48%, 27.6 mmol) was added and the mixture was stirred at 160°C for 1.5 hrs. Brine-ice was added to quench the reaction, and then the solution was extracted with methylene chloride (50 ml x 4). The combined extract was washed with brine, water, sat. $NaHCO_3$, dried over anhydrous magnesium sulfate and activated carbon (Darco-60). It was poured on a silica gel pad (5 cm x 5 cm), washed with methylene chloride and then EtOAc, to

give a syrup which from 95% EtOH, 13 (1.3 g, 49.8%) was crystallized. m.p. 77-78°C; lit.: 82°C.

^{1}H-NMR($CDCl_3$): δ 7.314, 8.146 (m, 15H, OBz); 6.757 (d, J=9.1Hz, 1H, H-1); 5.38 (d, J=48.5Hz, 1H, H-2); 5.630 (dd, J=22.5Hz, 1H, H-3); 4.768 (m, 3H, H-4 and H-5).

N_9-[3',5'-Di-O-benzoyl-2'-deoxy-2'-fluoro-β-L-arabinofuranosyl]-2,6-di-chloro-purine (15)

Compound 13 (464 mg, 1 mmol) was dissolved in 10 ml of methylene chloride while 1.4 ml of HBr/AcOH (45% w/v) was added. The solution was stirred at r.t. for 24 hrs, and then evaporated to dryness. The residue was dissolved in 20 ml of methylene chloride, and washed with water, sat. $NaHCO_3$, dried ($MgSO_4$). Filtration and evaporation gave the bromosugar 14 (100%, based on TLC).

At the same time, 2,6-di-chloro-purine (378 mg, 2 mmol) was suspended in 15 ml of HMDS and 2 mg of ammonium sulfate, and then refluxed for 2 hrs. The HMDS was evaporated with high vacuum under N_2 to give the white silylated base.

The bromosugar 14 was dissolved in 25 ml of anhydrous 1,2-dichloroethane. The resulting solution was added to the silylated base under N_2. The mixture was stirred under reflux for 2 days. Chloroform (30 ml) was added, and then washed successively with water (20 ml x 2), sat. $NaHCO_3$(20 ml x 2), sat. NaCl solution (20 ml x 2), and dried ($MgSO_4$). From $CHCl_3$, compound 15 (105 mg, 19.7%) crystallized. m.p. 158°C; D form: 158°C. UV(Methanol): λ_{max}: 238.50 nm, 273.0 nm.

^{1}H-NMR (300MHz, DMSO-d_6): δ 8.82 (d, J=1.5Hz, 1H, H-8); 7.49, 8.33 (m, 10H, OBz); 6.767 (dd, J_{H-H}=4Hz, K_{F-H}=13.8Hz, 1H, H-1'); 5.854 (dq, J=67.4Hz, 1H, H-2'); 5.910 (m, 1H, H-3'); 4.751 (m, 3H, H-4' and H-5').

N_9[2'-deoxy-2'-fluoro-β-L-arabinofuranosyl]-2,6-di-chloropurine (16)

Compound 15 (70 mg, 0.13 mmol) was dissolved in 25 ml of sat. NH_3/CH_3OH in a sealed steel bomb and heated at 90°C for 6 hrs. Removal of solvent under reduced pressure gave a yellow semisolid which was purified by preparative TLC (9:1/$CHCl_3$:CH_3OH). Lyophilization from water and 1,4-dioxane gave a white powder 16 (30 mg, 75%). UV(H_2O) pH2, λ_{max} 212.00 nm, 263.50 nm (ε6711); pH7, λ_{max} 213.50nm, 263.00nm (ε7590); pH11, λ_{max} 213.5nm, 263.00nm (ε5468).

^{1}H-NMR (300MHz, DMSO-d_6): δ 8.279 (d, J=1.5Hz, 1H, H-8); 7.908 (bs, 2H, NH_2); 6.321 (dd, J_{H-H}=4.4Hz, J_{F-H}=13.8Hz, 1H, H-1'); 5.986 (t, 1H, 5'-OH); 5.230 (dt, J_{F-H}=52.6Hz, 1H, H-2'); 5.115 (d, 1H, 3'-OH); 4.425 (dq, J_{F-H}=19Hz, 1H, H=3'); 3.841 (m, 1H, H-4'); 3.636 (d, 2H, H-5').

N_1-(2'-Deoxy-2'-fluoro-3',5'-di-O-benzyl-β-L-arabinofuranosyl)-thymine (17)

To a solution of 13 (400 mg, 0.86 mmol) in anhydrous CH_2Cl_2 (10 ml) was added hydrogen bromide in acetic acid (45% w/v, 1.5 ml), and the resulting solution was stirred at r.t. for 17 hrs. After evaporation of the solvent and coevaporation with toluene, compound 14 was obtained.

At the same time, thymine (215 mg, 1.72 mmol) was refluxed in HMDS (25 ml) under nitrogen for 17 hrs, to get a homogeneous solution. Evaporation of the solvent gave a silylated thymine.

A solution of 14 in dichloroethane (50 ml) was added to the silylated thymine and the resulting solution was refluxed under nitrogen for 3 days. Water was added and then extracted with $CHCl_3$. The organic layer was washed with water, brine and dried ($MgSO_4$). Evaporation of the solvent gave the

crude product, which was purified on preparative TLC using 2% MeOH/$CHCl_3$ to give 17 (235 mg, 58%). m.p. 99-101°C. UV(Methanol): 230, 264 nm $[\alpha]_D$=+22.397.

^{1}H-NMR($CDCl_3$): δ 7.343-8.389 (m, 12H, Ar-H, NH); 6.34 (dd, J_{H-H}=2.97Hz, J_{F-H}=28.32Hz, 1H, H-1'); 5.383 (dd, J_{H-H}=2.7Hz, J_{F-H}=63.27Hz, 1H, H-2'); 5.565 (dd, 1H, H-3'); 4.812 (d, 2H, H-5'); 4.466 (m, 1H, H-4'); 1.775 (s, 3H, CH_3). Anal. ($C_{24}H_21N_2O_7F$), C: 61.01; H, 4.57; N: 5.73; F: 3.92.

N_1-(2'-Deoxy-2'-fluoro-β-L-arabinofuranosyl)-thymine (18)

Compound 17 (145 mg, 0.309 mmol) was treated with NH_3/CH_3OH at r.t. for 18 hrs. After evaporation of the solvent and purification on preparative TLC (15% MeOH/$CHCl_3$, 18 (70 mg, 87.5%) was obtained. m.p. 174-175°C. UV: 264 nm, $[\alpha]_D$=-104.36.

H-NMR (DMSO-d_6): δ 11.401 (s, 1H, NH); 7.575 (s, 1H, H-6); 6.093 (dd, J_{H-H}=4.41Hz, J_{F-H}=15.6Hz, H-1'); 5.844 (d, 1H, 3'-OH); 5.019 (dt, J_{F-H}=53.3Hz, 1H, H-2'); 5.087 (t, 1H, 5'-OH); 4.194 (dq, 1H, H-3'); 3.647 (m, 3H, H-4' and H-5'); 1.781 (s, 3H, CH_3). Anal. ($C_{10}H_{13}N_2FO_5$), C: 44.80; H: 4.97; N: 10.04; F: 7.03.

N_1-(2'-Deoxy-2'-fluoro-3',5'-di-O-benzoyl-β-L-arabinofuranosyl)-5-ethyluracil (19)

To a solution of 13 in anhydrous dichloromethane (10 ml) was added hydrogen bromide in acetic acid (45% w/v, 0.97 ml, 5.385 mmol). The solution was stirred at r.t. for 18 hrs, after evaporation of the solvent and coevaporation with toluene, 14 was obtained.

At the same time, 5-ethyluracil (0.75 g, 5.39 mmol) was suspended in HMDS (10 ml) with ammonium

sulfate (5 mg) and refluxed for 5 hrs. under nitrogen to give a homogeneous solution.

The silylated base solution was evaporated to dryness with avoiding the contact of moisture. To the obtained syrup was added a solution of 14 in anhydrous 1,2-dichloroethane (10 ml). The reaction mixture was stirred at 95°C under nitrogen for 20 hrs, then evaporated under vacuum to dryness to give a yellow solid, which was mixed with 5 ml of $CH_3OH/CHCl_3$ (1:1) and filtered. The filtrate was evaporated to give a residue, which was chromatographed on silica gel column ($CH_3OH/CHCl_3$, 0-1%) to give a white solid 19 (0.557 g, 100%).

^{1}H-NMR (DMSO-d_6): δ 11.55 (s, 1H, NH); 7.51, 8.08 (m, 10H, Ar-H); 7.32 (s, 1H, H-6); 6.29, 6.37 (dd, J_{H-H}=3.7Hz, J_{F-H}=20Hz, 1H, H-1'); 5.68-5.75 (dd, J_{F-H}=20Hz, 1H, H-3'), 5.47-5.65 (dd, J_{F-H}=54Hz, 1H, H-2'); 4.62-4.83 (m, 3H, H-4' and H-5'); 2.01, 2.09 (q, 2H, $\underline{CH_2}$-CH_3); 0.85 (t, 3H, CH_3).

N_1-(2'-Deoxy-2'-fluoro-β-L-arabinofuranosyl)-5-ethyluracil (20)

Compound 19 (500 mg) was dissolved in methanolic ammonia (50 ml) and stirred at r.t. for 44 hrs. The solution was evaporated to dryness to give a white solid (0.4 g), which was chromatographed on silica gel column. (CH3OH/CHCl3, 0-5%) to give a white solid 20 (240 mg, 84%). m.p. 158-161°C. UV(MeOH): λ_{max} 260 nm.

^{1}H-NMR (DMSO-d_6): δ 11.42 (s, 1H, NH); 7.57 (s, 1H, H-6'); 6.10, 6.17 (dd, J_{H-H}=5.0Hz, J_{F-H}=14Hz, 1H, H-1'); 5.88 (bs, 1H, 3'-OH); 5.14, 5.19 (m, 2H, H-2' and 5'-OH); 4.98 (t, 1H, H-3'); 4.22, 4.28 (m, 1H, H-4'); 3.55, 3.78 (m, 2H, H-5') Anal. ($C_{11}H_{15}N_2O_5F$): C: 47.93; H: 5.56; N: 10.06; F: 6.68.

N_1-(2'-Deoxy-2'-fluoro-3',5'-di-O-benzoyl-β-L-arabinofuranosyl)-N^4-benzoyl-5-iodocytosine (21)

To a solution of 13 (150 mg, 0.323 mmol) in anhydrous methylene chloride (5 ml) was added hydrogen bromide in acetic acid (45% w/v, 0.29 ml, 1.615 mmol). The reaction mixture was stirred at r.t. for 9.5 hrs. After evaporating the solvent and coevaporating with toluene, 15 was obtained as a yellow syrup.

At the same time, N^4-benzoyl-5-iodocytosine (550 mg, 1.615 mmol) was suspended in HMDS (8 ml) with ammonium sulfate (3 mg) and refluxed for 5 hrs. under nitrogen to give a homogeneous solution.

The silylated base solution was evaporated to dryness with avoiding the contact of moisture. To the obtained syrup was added a solution of 14 in anhydrous 1,2-dichloroethane (10 ml). The reaction mixture was refluxed under nitrogen for 23 hrs, then evaporated to dryness to give a brown syrup, which was triturated with chloroform (30 ml). The resulting precipitate was filtered off and washed with chloroform. The filtrate and washings were combined and evaporated to give a brown syrup. The product mixture was separated by chromatography on silica gel column ($CH_3OH/CHCl_3$, 0-1%) to give a white solid 21 (100 mg, 45%).

^{1}H-NMR ($CDCl_3$): δ 11.40 (bs, 1H, NH): 7.26, 8.20 (m, 17H, Ar-H, H-6 and NH); 6.36, 6.44 (dd, J_{HH}=2.8Hz, J_{F-H}=21Hz, 1H, H-1'); 5.62, 5.68 (dd, 1H, H-3'); 5.39, 5.56 (dd, 1H, H-2'); 4.58, 4.85 (m, 3H, H-4' and H-5').

N_1-(2'-Deoxy-2'-fluoro-β-L-arabinofuranosyl)-5-iodocytosine (22)

Compound 21 (100 mg, 0.27 mmol) was treated with sat. NH_3/MeOH (60 ml) at r.t. for 24 hrs. Silica gel column chromatography (0-10% $CH_3OH/CHCl_3$) gave

compound 22 (35 mg, 71%) as a white solid. $[\alpha]_D$=-65.4 (c 0.34, CH_3OH); UV(MeOH): λ_{max}=293 nm.

^{1}H-NMR (DMSO-d_6); δ 8.04 (s, 1H, H-6); 6.74, 7.94 (s, 1H, NH); 6.01, 6.08 (dd, J_{H-H}=3.9Hz, J_{F-H}=16.6Hz, 1H, H-1'); 5.85 (d, 1H, 3'-OH); 5.17 (t, 1-H, 5'-OH); 5.08 (t, 1H, H-2'); 4.89 (t, 1H, H-3'); 4.15-4.23 (m, 1H, H-4'); 3.63-3.79 (m, 2H, H-5').

N_1-(2'-Deoxy-2'-fluoro-3',5'-di-O-benzoyl-β-L-arabinofuranosyl)-5-iodouracil (23)

To a solution of 13 (260 mg, 0.56 mmol) in 10 ml of anhydrous CH_2Cl_2 was added HBr/AcOH (45%, w/v, 0.5 ml, 2.8 mmol). The reaction mixture was stirred at r.t. for 36 hrs, and then evaporated to dryness. The residue was dissolved in 20 ml of CH_2Cl_2, washed with water (10 ml), sat. $NaHCO_3$ (10 ml) and dried ($MgSO_4$). Filtration and evaporation gave the bromosugar 14 as a syrup.

At the same time, 5-iodouracil (270 mg, 1.12 mmol) was suspended in 10 ml of HMDS and refluxed for 36 hrs. to give a homogeneous solution. It was evaporated under vacuum to dryness. To this was added a solution of 14 in anhydrous 1,2-dichloroethane, and the resulting solution was refluxed under N_2 for 1.5 days. $CHCl_3$ (20 ml) was added, and the solution was washed successively with water (10 ml), brine (10 ml) and sat. $NaHCO_3$ (10 ml) and then dried ($MgSO_4$). Removal of solvent gave a syrup which was crystallized in CH_2Cl_2 to give 23 as a yellow solid (237 mg, 73%). A part of this (70 mg) was recrystallized from 2-isopropanol to give a white solid (67 mg). UV(Methanol): λ_{max} 230.0 nm, 276.0 nm.

^{1}H-NMR ($CDCl_3$): δ 8.4, 7.3 (m, 12H,Ar-H); 6.29 (dd, J_{H-H}=2.43Hz, J_{F-H}=21.6Hz 1H, H-1'); 5.377 (dd, J_{H-H}=2.8Hz, J_{F-H}=61.3Hz, 1H, H-2'); 5,55 (dd, 1H, H-3'); 4.865, 4.793 (d, 2H, H-5'); 4.588, 4.502 (m, 1H, H-4').

N_1-(2'-deoxy-2'-fluoro-β-L-arabinofuranosyl)-5-iodouracil (24)

Compound 23 (40 mg, 0.069 mmol) was dissolved in 25 ml of sat. NH_3/MeOH and stirred at r.t. for 24 hrs, and then evaporated to dryness. The resulting syrup was purified on preparative TLC (5:1/$CHCl_3$:MeOH) to give 24 as a solid (19 mg, 74%). UV(MeOH): λ_{max} 280.5 nm.

^{1}H-NMR (DMSO-d_6): δ 11.82 (bs, CONH); 8.24 (s, 1H, H-6); 6.082 (dd, J_{H-H}=4.45 Hz, J_{F-H}=13.7 Hz, 1H, H-1'); 5.947 (d, 1H, 3'-OH); 5.296 (t, 1H, 5'-OH); 5.07 (dt, J_{F-H}=53 Hz, 1H, H-2'); 4.24 (bd, J_{F-H}=21 Hz, 1H, H-3'); 3.81, 3.55 (m, 3H, H-4', H-5').

2,3,5-Tri-O-benzyl-L-arabinose

As illustrated in Figure 9, thirty grams (0.2 mol) of powdered L-arabinose (5) and then 0.4 ml of concentrated sulfuric acid were added to 600 ml (14.8 moles) of anhydrous methanol. The suspension was stirred and heated under gentle reflux to give a clear solution for 2 hrs. The reaction mixture was neutralized with 1.5 g sodium hydrogen carbonate, dried (Na_2SO_4), and then evaporated *in vacuo* to give a heavy syrup 6 which was diluted with 50 ml of freshly purified tetrahydrofuran and reconcentrated (35-40° bath) to remove residual methanol. Freshly purified tetrahydrofuran (400 ml) was added, and the mixture treated with 30 g. of Drierite, 156 g (2.78 mole) of potassium hydroxide, and 200 ml (1.74 mole) of benzyl chloride. The mixture was heated under gentle reflux overnight, cooled, filtered through a thin layer of Celite, and concentrated *in vacuo*, and then at high vacuo and 100° (bath). The crude, syrupy methyl 2,3,5-tri-O-benzyl-L-arabinoside (7) was dissolved in 400 ml of glacial acetic acid. The hydrolysis mixture is heated at 65-70° for 2

hrs, concentrated *in vacuo* to one-third its volume, and poured into 2.5 L of a mixture of ice water. After being seeded (seeded crystals were originally obtained by chromatography being eluted with dichloromethane), the mixture was kept at 5° overnight. The aqueous layer was decant from the partially crystalline mass, and the latter was dissolved in 200 ml of dichloromethane. The solution was washed with cold, aqueous sodium hydrogen carbonate, dried (Na_2SO_4), filtered through a thin bed of decolorizing carbon, and concentrated *in vacuo* to a thin syrup which was dissolved in 200 ml of cyclohexane. After being seeded[5], the solution was kept at room temperature for 1 hr. and at 5° overnight, to give 27.7 g (33.2%) of 2,3,5-tri-O-benzyl-L-arabinose (8). m.p. 68-73°C. $[\alpha]^{25}_D$=-1.69 [C 2.01, 9:1 (v/v p-dioxane-water)] UV(MeOH) λ_{max} 220; 300-MHz 1HNMR($CDCl_3$) δ 3.48-3.62(m,2H,H-5), 3.94-4.18(m,3H,H-2,3,4), 5.33(d,1H,J=4.07,H-1), 5.29(s,H-1), 7.25-7.33(m,15,H-aromat).

2,3,5-Tri-O-benzyl-1-O-(p-nitrobenzoyl)-L-arabinose (9)

Compound 8 (Figure 9) (2 g, 4.76 mmole) was dissolved in 7.5 ml of dichloromethane, and to this solution was added a solution of 0.95 g (5.1 mmoles) of p-nitrobenzoyl chloride in a mixture of 5 ml dichloromethane and 1.5 ml of pyridine. The reaction mixture was kept at room temperature overnight, and was then washed successively with 1N hydrochloric acid (2 X 10 ml), aqueous sodium hydrogen carbonate (2 X 10 ml), and water (3 X 30 ml). Moisture was removed with Na_2SO_4, and the solution was concentrated *in vacuo* to give 2.67 g (98.4%) of a mixture of the anomers of compound 9. mp 68-82°C. Further purification by silica gel column chromatography (hexanes:acetone, 8:1) raise

the mp to 89-93°C; $[\alpha]^{24}_{D}$=13.04(C6.8, CH_2Cl_2), UV(MeOH) λ_{max} 215.5 and 258.5, 250MHz 1NMR(CDCl3): δ 3.54-3.69 (m, 2H, H-5), 4.06 (m, 1H, H-4'), 4.22 (m, 1H, H-3'), 4.33 (m, 1H, H-2'), 4.38-4.78 (m, 6H, benzyl CH_2), 6.50 (d, 1H, J=2.35, H-1), 7.23-7.36 (m, 15H, H-aromat of benzyl group), 8.01-8.25 (m, 4H, H-acromat of nitrobenzoyl group).

10(2,3,5-Tri-O-benzyl-β-L-arabinosyl) thymine (12)

Thymine 0.444 g (3.52 mmole) and ammonium sulfate (2 mg) were suspensed in hexamethyldisilazane 10 ml, which was refluxed (140°C) overnight under argon to give a clear solution. Excess hexamethyldisilazane was removed *in vacuo* while avoiding of contact of moisture to give a syrup 11.

Compound 9 (1 g, 1.76 mmole) was added to 17 ml of dichloromethane presaturated with anhydrous hydrogen chloride at 0°C. After 2 h at 0°C, the precipitated p-nitrobenzoic acid (0.25 g) was removed by filtration, and the filtrate was concentrated *in vacuo* to a thin syrup, and then kept at high vacuo pump at room temperature for 2 hours to give 2,3,5-tri-O-benzyl-α-L-arabinosyl chloride (10).

Compound 10 thus prepared was dissolved in 15 ml of anhydrous dichloromethane, and the solution was added to a mixture of silylated thymine (11) and 3 g of 4A molecular sieve. The reaction mixture was stirred at room temperature under argon for 18h. The reaction mixture was diluted with 50 ml of dichloromethane, and poured into 2 ml of saturated aqueous $NaHCO_3$ under vigorous stirring. White precipitate (tin hydroxide) appeared, which was filtered out on the bed of celite. The organic layer was separated from water and washed with water (3 X 30 ml). The aqueous layer was extracted with dichloromethane, and the combined

dichloromethane layer was dried over Na_2SO_4, and then evaporated *in vacuo* to give a syrup which was purified by silica gel column chromatography (chloroform:methanol, 100:1) to give 12 as a syrup 0.68g (73%): $[\alpha]^{25}_D$=-56.71 (C 0.6, CH_2Cl_2). UV(MeOH) λ_{max} 218 and 265; 300MHz 1HNMR($CDCl_3$): δ 1.67 (d,3H,J=1.11,CH_3), 3.66-3.70 (m, 2H, H-5') 4.06 (m, 1H, H-4'), 4.13 (t, 1H, J=4.7, H-3'), 4.24 (t, 1H, J=4.7, H-2'), 4.41, 4.54, 4.56 (m, 6H, benzyl CH_2), 6.28 (d, 1H, J=5.24, H-1'), 7.15-7.33 (m, 15H, H-aromat), 7.43 (d, 1H, J=1.31, H-6).

1-β-L-arabinofuranosylthymine (13)

Palladium chloride (680 mg, 3.835 mmole) was suspended in 100 ml of methanol, and reduced by shaking with hydrogen at room temperature. A solution of 450 mg of 12 in 25 ml of methanol was then added to the acidic suspension of palladium black. The reaction mixture was shaken with hydrogen at room temperature for 38 hrs. After the catalyst had been removed, the solution was neutralized with Dowex (HCO_3^-) to pH 7 and concentrated *in vacuo* to a white solid which was recrystallized with ethanol to give 13 (105 mg, 47.7%). m.p. 244-249°C. $[\alpha]^{25}_D$=-91.48 (0.25, H2O); IR(KBr): 1750, 1600cm^{-1}(CO); UV(MeOH): λ_{max} 268; 300 MHz 1HNMR(DMSO-d_6): δ: 1.76 (s, 3H, CH_3), 3.62 (t, 2H, J=4.56, H-5') 3.69 (m, 1H, H-4'), 3.90 (t, 1H, J=3.88, H-3'), 3.99 (t, 1H, J=4.10, H-2'), 5.08 (br s, 1H, C'5-OH, exchangeable), 5.42 (d, 1H, J=4.24, C'2-OH or C'3-OH, exchangeable), 5.54 (d, 1H, J=5.23, C'2-OH or C'3-OH, exchangeable), 5.97 (d, 1H, J=4.64, H-1'), 7.51 (d, 1H, J=0.97, H-6), 11.26 (s, 1H, NH, exchangeable). Anal. Calcd. for $C_{10}H_{14}N_2O_6$; C, 46.51; H, 5.46; N, 10.85; found: C, 46.67; H, 5.63; N, 10.56.